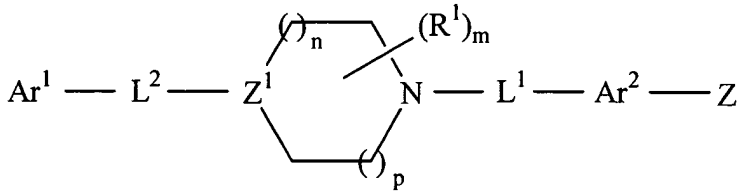
Claims

1. A compound of the formula:



and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein:

Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

each R^1 is independently a noninterfering substituent;

Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent;

m is 0-4;

each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;

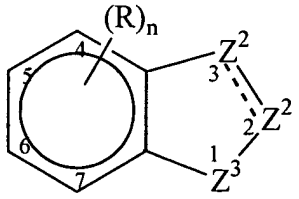
Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is $-W_i-COX_jY$ wherein Y is COR^3 or an isostere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space

between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms;

with the proviso that the portion of the compound represented by Ar^2-Z is not



wherein ⫽ represents a single or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is $-W_i-COX_jY$ wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1; Z^3 is NR or O; and each R is independently hydrogen or a noninterfering substituent.

2. The compound of claim 1 wherein said smallest number of bonds is 6-12.

3. The compound of claim 1 wherein Z is $COXjCOR^3$, and

wherein R^3 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, SOR, SO_2R, SO_2NR_2, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, CN, COOR, $CONR_2$, COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or

wherein R^3 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$, or $NRSO_2NR_2$, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member carbocyclic or heterocyclic ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined; and

X, if present, is CR_2 where R is as defined above.

4. The compound of claim 1 wherein Y is an isostere of COR^3.

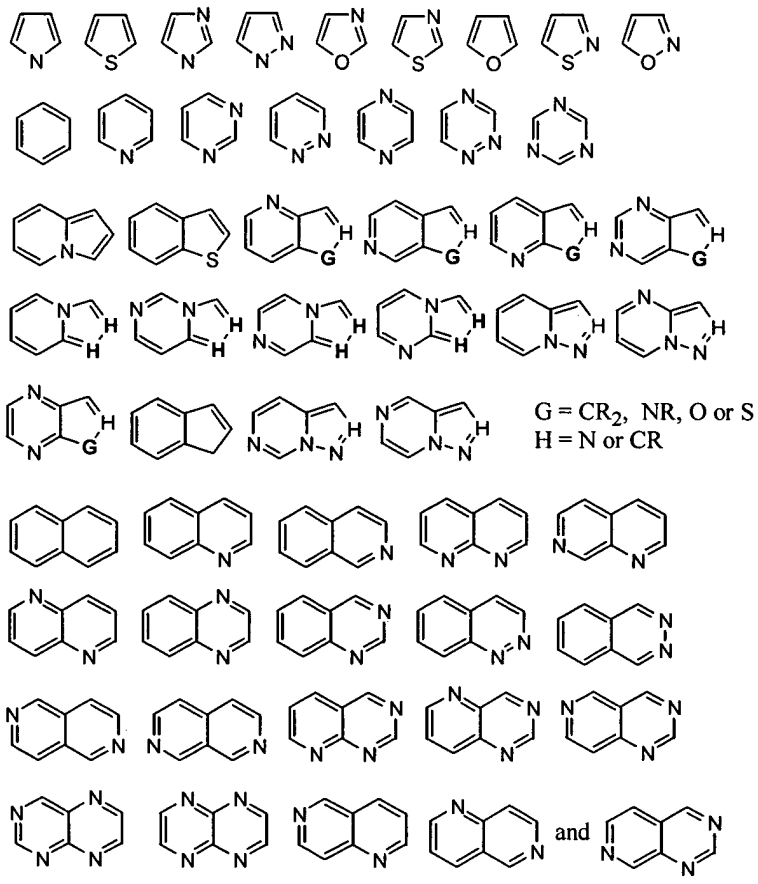
5. The compound of claim 4 wherein Y is tetrazole; 1,2,3-triazole; 1,2,4-triazole; or imidazole.

6. The compound of claim 1 wherein each of i and j is 0.

7. The compound of claim 3 wherein j is 0.

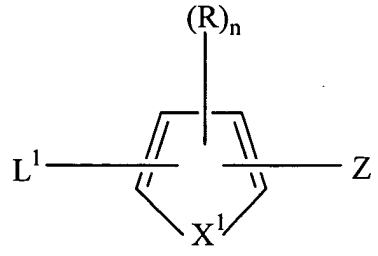
8. The compound of claim 1 wherein $-Ar^2-$ comprises an optionally substituted monocyclic or polycyclic aromatic nucleus, wherein said aromatic nucleus consists of carbocyclic or heterocyclic ring selected from (i) a five-membered heterocyclic or carbocyclic ring (ii) a six-membered carbocyclic or heterocyclic ring; (iii) a five-membered carbocyclic or heterocycloc ring fused to another five-membered carbocyclic or heterocyclic ring; (iv) a six-membered carbocyclic or heterocyclic ring fused to another six-membered carbocyclic or heterocyclic ring; and (v) a five-membered heterocyclic or carbocyclic ring fused to a six-membered carbocyclic or heterocyclic ring.

9. The compound of claim 8 wherein Ar^2 is selected from:



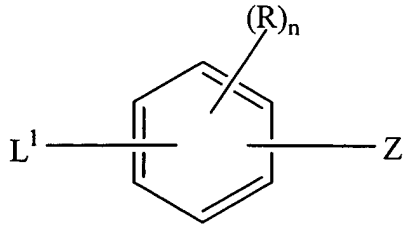
where R is a noninterfering substituent.

10. The compound of claim 8 wherein the portion of said compound represented by L^1-Ar^2-Z is selected from the following:



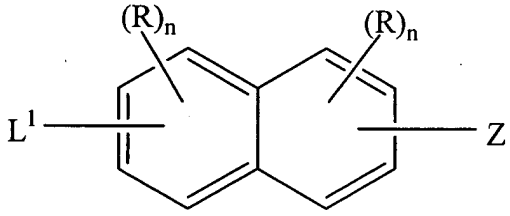
(I)

wherein n is 0, 1 or 2; X^1 is NR, CR_2, O or S; and each R is independently H or a noninterfering substituent; and two or more R groups may form a fused ring;



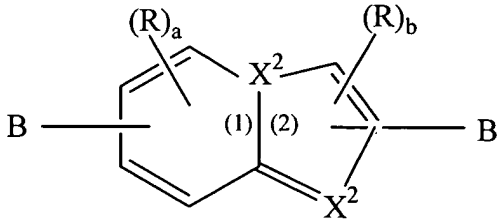
(II)

wherein n is 0-4; R is H or a noninterfering substituent where two or more R groups may form a fused ring; and one or more ring carbons may be optionally replaced with nitrogen;



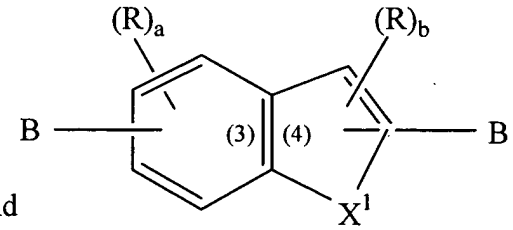
(III)

wherein each n is inpendently 0 to 3; R is H or a noninterfering substituent, where two or more R groups may form a fused ring; and one or more ring carbons may be optionally replaced with nitrogen;



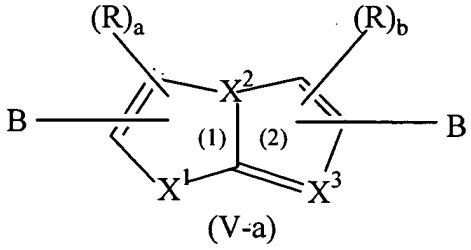
(IV-a)

and



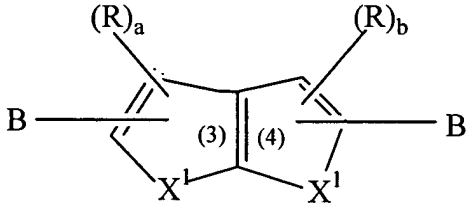
(IV-b)

wherein, subject to the proviso of claim 1, one B is L^1 and the other is Z; wherein a is 0 to 4 such that the positions on the six membered rings (1) and (3) to which $(R)_a$ is bonded can include X^2 when X^2 is C; b is 0 –3 such that the positions on the five-membered rings (2) and (4) to which $(R)_b$ is bonded can include X^2 and X^1, when X^2 is C and X^1 is N or C; each X^2 is independently N or CR; $X^1$is NR, CR_2, O or S; each R is H or a noninterfering substituent where two or more R groups may form a fused ring; wherein one or more of the ring carbons that are at positions other than X^2 or X^1 and that are also not bound to B can be optionally replaced with N;



(V-a)

and



(V-b)

wherein one B is L^1 and the other is Z; a is 0-4 such that the positions on the rings (1) and (3) to which $(R)_a$ can be bonded include X^2 and X^1 where X^2 is C and X^1 is C or N; b is 0 or 3 such that the positions on the rings (2) and (4) to which $(R)_b$ can be bonded include X^1, X^2 and X^3 when X^1 is C or N and X^2 and/or X^3 are C; each X^1 is independently NR, $C(R)_2$, O or S; X^2 and X^3 are independently N or CR; each R is independently H or a noninterfering substituent where two or more R groups can optionally form a fused ring; wherein one or more of the ring carbons that are at positions other than X^1, X^2 or X^3, and that are also not bound to B, can be optionally replaced with N.

11. The compound of claim 10 wherein L^1-Ar^2-Z is structure (I).

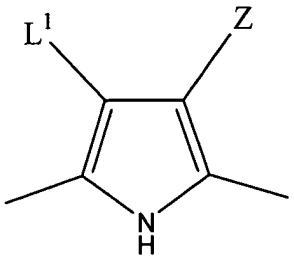
12. The compound of claim 11 wherein X^1 in structure (I) is NR.

13. The compound of claim 12 wherein X^1 in structure (I) is NH.

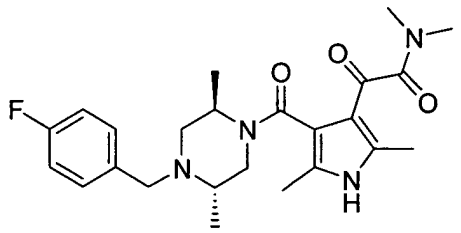
14. The compound of claim 13 wherein R is methyl.

15. The compound of claim 14 wherein n is 2.

16. The compound of claim 15 wherein structure (I) is:



17. The compound of claim 16 where the compound is:

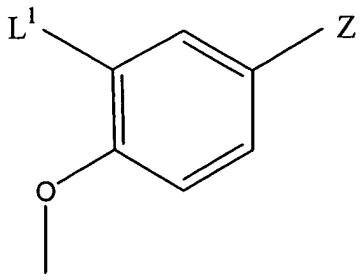


10. The compound of claim 10 wherein L^1-Ar^2-Z is structure (II).

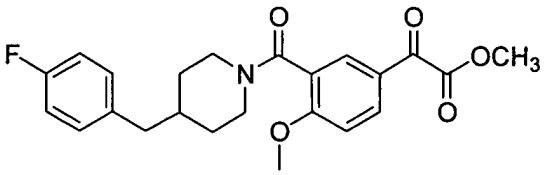
19. The compound of claim 18 wherein the R in structure (II) is methoxy.

20. The compound of claim 19 wherein n in structure (II) is 1.

21. The compound of claim 20 wherein structure (II) is



22. The compound of claim 21 wherein the compound is:

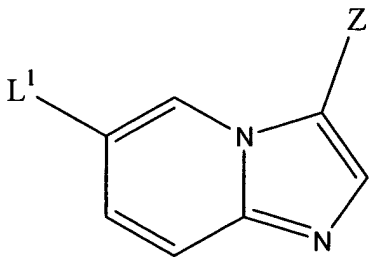


23. The compound of claim 10 wherein L^1-Ar^2-Z is structure (III).

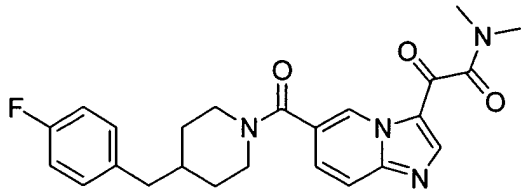
24. The compound of claim 10 wherein L^1-Ar^2-Z is structure (IV-a) or (IV-b).

25. The compound of claim 24 wherein L^1-Ar^2-Z is (IV-a) and both X^2 in structure (IV-a) are nitrogen.

26. The compound of claim 25 wherein structure (IV) is:



27. The compound of claim 26 wherein the compound is:



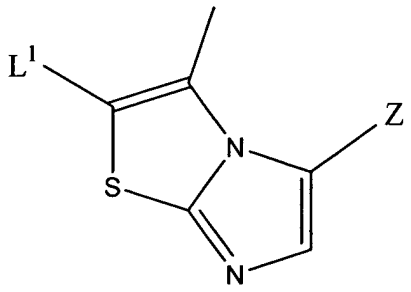
28. The compound of claim 8 wherein L^1-Ar^2-Z is structure (V-a) or (V-b).

29. The compound of claim 28 wherein L^1-Ar^2-Z is structure (V-a) and X^2 and X^3in structure (V-a) are N.

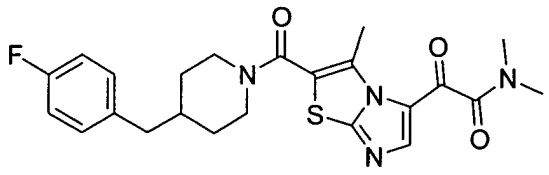
30. The compound of claim 29 wherein at least one R in structure (V) is methyl.

31. The compound of claim 29 wherein X^1 in structure (V) is S.

32. The compound of claim 31 wherein structure (V) is:



33. The compound of claim 32 wherein the compound is:



34. The compound of claim 1 wherein both n and p are 1.

35. The compound of claim 1 wherein L^1 is CO, CHOH or CH_2.

36. The compound of claim 35 wherein L^1 is CO.

37. The compound of claim 1 wherein Z^1 is N.

38. The compound of claim 1 wherein Z^1 is CR^2 wherein R^2 is H, OR, NR_2, SR or halo, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof.

39. The compound of claim 1 wherein L^2 is alkylene (1-4C) or alkenylene (1-4C) optionally substituted with a moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on L^2 can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety.

40. The compound of claim 39 wherein L^2 is unsubstituted alkylene.

41. The compound of claim 39 wherein L^2 is unsubstituted methylene, methylene substituted with alkyl, or -CH=.

42. The compound of claim 1 wherein Ar^1 is optionally substituted with 0-5 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR,

$OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

43. The compound of claim 42 wherein Ar^1 is optionally substituted phenyl.

44. The compound of claim 43 wherein said optional substitution is by halo, OR, or alkyl.

45. The compound of claim 44 wherein said phenyl is unsubstituted or has a single substituent.

46. The compound of claim 1 wherein R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^4 on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or R^4 is =O or an oxime, oximeether, oximeester or ketal thereof.

47. The compound of claim 46 wherein each R^1 is halo, OR, or alkyl.

48. The compound of claim 47 wherein m is 0, 1, or 2.

49. The compound of claim 48 wherein m is 2 and both R^1 are alkyl.

50. The compound of claim 10 wherein each of the non-interfering groups R, when bonded to a ring carbon atom, are selected from the group consisting of:

(a) hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl and halo; or

(b) or from OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R in the preceding (b) selections is independently H, alkyl, alkenyl or aryl or heteroforms thereof;

and wherein two of the non-interfering groups R can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

51. The compound of claim 50 wherein the non-interfering groups R are independently selected from the group consisting of H, alkyl, acyl, aryl, arylalkyl, heteroalkyl, heteroaryl, halo, OR, NR_2, SR, NRCOR, alkyl-OOR, RCO, COOR, and CN, wherein each R is independently H, alkyl, or aryl or heteroforms thereof.

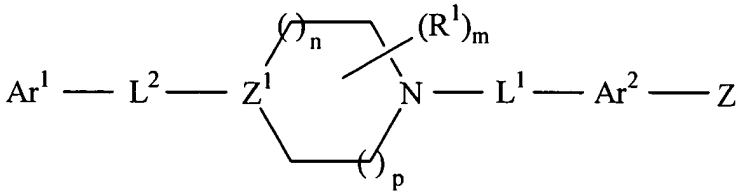
52. The compound of claim 10 wherein the noninterfering groups R, when bonded to a nitrogen ring atom, are selected from the group consisting of:

(a) H, or alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl; and

(b) SOR, SO_2R, RCO, COOR, alkyl-COR, SO_3R, $CONR_2$, SO_2NR_2, CN, CF_3, or R_3Si wherein each R in the preceding (b) selections is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

53. A pharmaceutical composition for treating conditions characterized by enhanced p38-α activity which composition comprises

a therapeutically effective amount of a compound of the formula



and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein:

Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

each R^1 is independently a noninterfering substituent;

Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent;

m is 0-4;

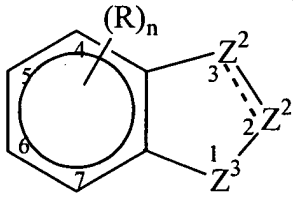
each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;

Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is $-W_i-COX_jY$ wherein Y is COR^3 or an isostere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms;

with the proviso that the portion of the compound represented by Ar^2-Z is not



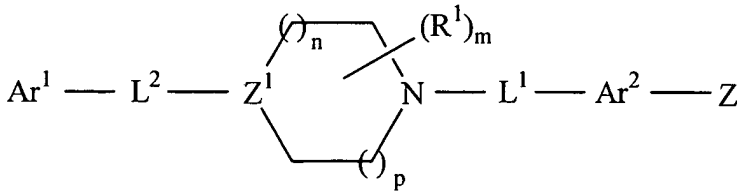
wherein ⩫ represents a single or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is $-W_i-COX_jY$ wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1; Z^3 is NR or O; and each R is independently hydrogen or a noninterfering substituent.

54. The pharmaceutical composition of claim 53 wherein said smallest number of bonds is 6-12.

55. The composition of claim 53 which further contains an additional therapeutic agent.

56. The composition of claim 55 wherein said additional therapeutic agent is a corticosteroid, a monoclonal antibody, or an inhibitor of cell division.

57. A method to treat a condition mediated by p38-α kinase comprising administering to a subject in need of such treatment a compound of the formula:



and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

each R^1 is independently a noninterfering substituent;

Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent;

m is 0-4;

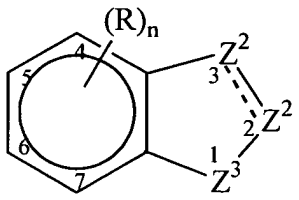
each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;

Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is $-W_i-COX_jY$ wherein Y is COR^3 or an isostere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms;

with the proviso that the portion of the compound represented by Ar^2-Z is not



wherein  represents a single or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is $-W_i-COX_jY$ wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1; Z^3 is NR or O; and each R is independently hydrogen or a noninterfering substituent.

58. The method of claim 57 wherein said smallest number of bonds is 6-12.

59. The method of claim 57 wherein said condition is a proinflammation response.

60. The method of claim 59 wherein said proinflammation response is multiple sclerosis, IBD, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, other arthritic conditions, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injury, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, a bone resorption disease, graft-versus-host reaction, Crohn's Disease, ulcerative colitis, Alzheimer's, pyresis or heart disease.